Factors modifying Drug Action

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FACTORS INFLUENCING DOSAGE AND DRUG RESPONSE

1. AGE , BODY WEIGHT AND BODY SURFACE AREA

-- avg. adult dose

1) YOUNG'S FORMULA :

applicable for children up to 12 yrs of age

$$\text{child's dose} = \frac{\text{age in yrs}}{\text{age} + 12} \times \text{adult dose}$$

2) DILLING'S FORMULA :

assumption that 20 yr old should receive an adult dose

$$\text{child's dose} = \frac{\text{age in yrs}}{20} \times \text{adult dose}$$

3) CLARK'S FORMULA :

based on proportional body wgt as related to an avg. adult weighing about 70 kg.

$$\text{Child's dose} = \frac{\text{wt. of child (kg)}}{70} \times \text{adult dose}$$

BUT, For an abnormally lean or obese individual

Body surface area à based on height and wgt à more precise index

- Child's dose = $\frac{\text{BSA (m2)}}{1.8}$ x adult dose

Dubois FORMULA

$$\text{BSA (m2)} = w^{0.425} (\text{kg}) \times H^{0.725} (\text{cm}) \times 0.00718$$

- NOMOGRAMS

- If not available,

- (1.5 x wt in kg) + 10 = % of adult dose to be given to the child

- INFANTS AND CHILDREN ARE NOT SMALL ADULTS

NEW BORN

-- drug *absorption* may also be altered due to lower gastric acidity

-- hepatic drug *metabolizing* system is inadequate e.g. gray baby syndrome & kernicterus

-- after the first year of life, drug metabolism is often faster than in adults.

-- low *GFR* & tubular transport is immature

ELDERLY

- Slower absorption due to ↓ motility of and blood flow to intestines
- â hepatic microsomal drug metabolizing activity and liver blood flow
- Renal function progressively ↓
- lower PPB due to lower plasma albumin
- Responsiveness to certain receptors à altered (e.g. β receptors)

2. GENDER :

(A)Females :-

- Smaller Body Size à requires lower dose
- Subjective effect due to different mental state
- Maintenance therapy with **Digoxin**à ↑ Mortality
- **Androgens à Unacceptable**
- **Morphine & barbiturates à** excitation prior to sedation
- **Ephedrine à** produce more excitation and
- **Ketoconazole à** Galactorrhoea, M/C irregularities, libido.

GENDER

- **Females :-**
- **During Pregnancy à** Produces Teratogenicity
- **(i) Phenytoin sodium à** Microcephaly, Cleft palate, Hare Lips
- **(ii) Sodium valproate à** Neural Tube Defect (NTD, Spina Bifida)
- **3rd trimester of pregnancyà** marked & progressive changes
- (**i) GI motility Decreases à** Delayed in oral drug absorption
- (ii) **RBF à** eliminates polar drug rapidly
- (iii) **Hepatic microsomal enzyme induction à** drug metabolism become faster

GENDER

(B) Males :-

- **Clonidine, α– methyl dopa, β blockers, diuretics and** à loss of libido in men not in women
- **Ketoconazole à** Gynaecomastia, loss of libido, impotence
- **Estrogens à** Unacceptable to men

SPECIES AND RACE

- **(A) SPECIES :-**
- Differences in drug response among different species
- **(i) Rabbits :- Resistant to Atropine (Due to Atropinase enzyme)**
- **(ii) Rats / Mice :- Resistant to Digitalis**
- **(iii) Rats :- More sensitive to Curare than Cat**

(Differences important while extrapolating results from experimental animals to humans)

- **(B) Racial Differences among Human Beings**
- **(i) Black :** B-Blockers less effective as antihypertensives
- **(ii) Mongolians :-** Requires lower concentrations of Atropine, Ephedrine for Pupil dilatation

- **(iii) Black :-** Requires higher concentration of Atropine & Ephedrine
- **(iv) Indians :-** Tolerates Thiacetazone better than whites
- (v) **Indians / Hongkong :-** Less incidences of Aplastic anaemia with Chloramphenicol than White

- (vi) **Japanese :-** Epidemic outbreak of SMON (Subacute Myo-optic Neuropathy) with Quinidochlor than Indians

3. ENVIRONMENT AND TIME OF DRUG ADMINISTRATION

-- higher doses of ***sedative hypnotics*** à needed to induce sleep in day light than at night.

-- ***high altitudes*** , capacity of body to oxidize drugs (phase I metabolism) is diminished, hence usual dosage may produce toxicity

- Exposure to insecticides, carcinogen, tobacco smoke à induces drug metabolism
- Glucocorticoids à single morning dose à minimizes chances of Pituitary adrenal axis suppression
- Statins (Atorvastatin, Simvastatin) à more effective if given at night as hypolipidemic agents.
- Food – drug interaction à affects drug absorption
- (i) Food decreases absorption of Ampicillin
- (ii) Fatty meals **enhances** absorption of Griseofulvin, Lumefantrine

4. PSYCHOLOGICAL AND EMOTIONAL FACTORS

- Patient's beliefs, attitudes and expectations à affects drug response
- **PLACEBO** (I shall Please) – **Physician-Patient** Relationship
- **Inert substance with no pharmacological action**
- Acts by suggestion (**Psychodynamic** than **Pharmacodynamic**)à induces psychological response
- **Produces response equivalent to active drug**
- **USED** in **2** situations :-
- (i) As a **Dummy medicine** in clinical trials of a drug **in a control group**
- (ii) To treat patient who actually do not require any medications

- **Placebo à releases Endorphins in brain à causes analgesia**
- **Placebo à produces variable effect in same individual** (produces sleep on 1st night & not on subsequent nights)
- **Examples :- Lactose Tablets** & **Distilled water Inj.**

N O C E B O

- Opposite of Placebo
- **Have Negative Psychodynamic Effect** evoked by pessimistic attitude of patient or Loss of Faith in medication & / or Physician
- **Opposes Therapeutic Effects of Active M**edication

ROUTES AND FREQUENCY OF DRUG ADMINISTRATION

- **Governs speed and intensity of drug responses**

- **Streptomycin** à Half life 2-4 hrs à **yet for TB given once daily for initial 2-3 months**

- **Parenteral administration of drugs (IV,IM) à produces more rapid, pronounce & predictable drug action**
- **MAGNESIUM SULFATE**
  - -- Purgation à orally
  - -- Reduces swelling in sprain à locally
  - -- CNS depression & hypotensionà IV

- **OXYTOCIN**
  - – slow iv inj. à induction of labour
  - -- to control postpartum hemorrhage --IM
  - -- let down of milk from engorged breast (intranasal spray)

CUMULATION

- Imbalance between Rate of drug administration and Rate of drug elimination
- If, Rate of Drug Administration > Rate of drug Elimination à Drug accumulation occurs in body part / organ or tissue
- **(i) Chloroquine :-** prolonged administration à **Retinal damage**
- **(ii) Amiodarone :- Microdipostion in Cornea**
- **(iii) Emetine :-** Course not repeated within 6 weeks
- **(iv) Digoxin :- Full loading dose not to be given if Patient has received it in past week.**

MODIFIED DRUG EFFECTS AFTER REPEATED ADMINISTRATION OF A SINGLE DRUG

- Drug tolerance
- Drug resistance
- Drug allergy
- Cumulation

DRUG TOLERANCE:- (Refractoriness)

Repeated administration of a drug for prolong timeà reduction in drug response à requires higher doses to produce previous response.

Loss of therapeutic effect is known as
“ Refractoriness”

(i) Sulphonylureas à in T2DM
(ii) B- 2 Agonists (Salbutamol) à Br. Asthma

(It is Adaptive Biological Phenomenon)

A) INNATE (NATURAL OR CONGENITAL) TOLERANCE

Genetically determined lack of sensitivity to drug

Observed very first time a drug is administered

Species tolerance

Rabbits are tolerant (Inheritantly less sensitive) **to large doses** of **Atropine** as they possess atropine esterase enzyme which rapidly detoxifies atropine.

Racial tolerance

Negros à tolerant to mydriatics – ephedrine, **atropine**

Black à Hyporesponsive to B.Blockers, alcohol

Chinese à tolerant to castor oil

B) ACQUIRED TOLERANCE:

seen by repeated uses of drug in individual who ***was initially responsive and takes weeks or months to develop tolerance.***

- Required to increase dose in order to produce pharmacological ***response of equal magnitude and duration.***

- **Drugs –**barbiturates, morphine , alcohol, amphetamine etc.

- Tolerance develop to sedative actions of ***phenobarbitone*** **but not to their antiepileptic effect.** (**Acquired** Tolerance)

- **Tolerance develop to sedative actions of** Chlorpromazine but not to its antipsychotic effect.(**Acquired** Tolerance)

- Tolerance develop to Euphoriant effect of ***morphine (may fail to produce euphoria),*** **But,** not to its **miotic and constipation effect** (can produce pinpoint pupil and constipation) **(Tissue Tolerance).**

- **CROSS TOLERANCE:**

- **Individual tolerant to particular group of drug also shows tolerance to other drugs belonging to the same group.**

-- individuals tolerant to **morphine** are also tolerant to heroin and other opioid analgesics like Tramadol, **Pentazocine.**

-- chronic alcoholics are more tolerant to General anaesthetics.

MECHANISM OF DEVELOPMENT OF DRUG TOLERANCE :-

(1) PHARMACOKINETIC TOLERANCE :- (DRUG DISPOSITIONAL / METABOLIC TOLERANCE)

Dispositional tolerance -> due to changes in drug P/Ks -> leads to decrease in intensity & duration of contact between drug & target tissue.

-- drug reduces its own absorption or increases its own metabolism through microsomal enzyme induction.

↓

↓ effective conc. of drug at site of action

Eg. Barbiturates, Carbamazepine à induces their own metabolism

- **Example of PK tolerance**

  -- ***due to poor absorption*** à **Alcohol.**

  -- ***due to increase metabolism*** through enzyme induction à **Barbiturates.**

  -- **due to enhanced drug elimination on chronic use à Decreases concentration of drug at site of action. (Amphetamineà Renal excretion accelerated after regular intake)**

-- ***due to faster excretion*** à amphetamine.

The drug *suppresses appetite* and **when the person continues taking the drug** in preference to food, ketosis results.

↓

-- ***Ketosis*** acidifies the urine and promotes ionization of drug leading to its ***faster excretion.***

↓

more dose is needed to produce the same ***euphoric effects.***

2) PHARMACODYNAMIC (Functional or Cellular or Target Tissue) TOLERANCE :-

- **Drug action decreases due to changes in the properties and functions of target tissue à makes less responsiveness or sensitive à associated with :- (either)**

a) drug induced changes in the receptor density **(down regulation)**

(or)

b) Impairment in receptor coupling to signal transduction pathways

Eg. Morphine, Barbiturates, Nitrates

-- Morphine and its congeners, caffeine, nicotine, barbiturates, alcohol

-- ***nitroglycerine tolerance*** among workers in its manufacturing industry.

TACHYPHYLAXIS

TACHYPHYLAXIS = Fast Protection (ACUTE TOLERANCE) :-

Acute development of tolerance after a ***rapid and repeated*** administration of a drug at ***shorter intervals*** ***resulting into progressive decrease in response to drug is known as Tachyphylaxis.***

Eg.

i) ***Ephedrine à produces diminished response in Broncial Asthma on repeated administration at short interval.***

ii) ***Tyramine à produces decrease response in BP in anaesthetized dog.***

Mechanisms of Action of Development of Tachyphylaxis :-

i) Gradual depletion of agonist **(Noradrenaline)** from storage sites.

(a) Indirectly acting sympathomimetics : -

Ephedrine, Tyramine, Amphetamine.

(b) lack of peripheral vasodilatation seen after repeated doses of **Morphine (at short intervals).**

(c) Slow dissociation of drug from its binding to the receptor à thus, continuing receptor blockade à while losing its intrinsic activity and Pharmacological effect (Isoprenaline).

TOLERANCE Vs. TACHYPHYLAXIS

--*Tolerance* develops slowly

observed with intermittent dosing schedules (e.g. after every 2nd or 3rd day)

--*Tachyphylaxis* develop faster

(due to quick repetition of doses)

-- In tolerance, original effect of drug can still be obtained by increasing dose

-- which is not possible in tachyphylaxis, either due to exhaustion of mediators or due to faster desensitization of target cells.

DRUG RESISTANCE :

unresponsiveness of microorganism to an antimicrobial agent after its repeated use.

1. NATURAL RESISTANCE

- M. Tuberculosis is insensitive to cephalosporin.
- poses no significant clinical problem

2. ACQUIRED RESISTANCE :

it is by an organism (***which was initially sensitive)*** due to use of an antimicrobial agent over a period of time.

e.g. antimicrobial agents à staphylococci, tubercule bacilli

- Develops either by

  gene transfer (conjugation, transduction or transformation)

  OR

  mutation

-- so overcome by either alternative drug or using a synergistic combination.

CROSS RESISTANCE:

- **DRUG ALLERGY**

  an adverse, ***unexpected response to the usual therapeutic doses*** of a drug resulting from ***previous exposure*** to the same substance.

CUMULATION :

- when rate of removal or inactivation of a drug is slower than the rate of its administration.

- lead to dangerous over dosage and toxicity

- E.g. digoxin, CHQ (retinal toxicity) , heavy metals like lead, à these drugs have long t1/2

- Certain highly lipid soluble drugs having shorter half lives e.g. thiopental à redistribution

- METABOLIC DISTURBANCES AND PATHOLOGICAL STATES

1) GIT DISEASES

(a) Coeliac dz : absorption of amoxicillin decrease cotrimoxazole increase.

(b) Achlorhydria à â aspirin absorption by favoring its ionization

-- low acidity à decrease iron (fe++) absorption and result in decrease response to iron therapy.

2) LIVER DISEASE:

--bioavailability increase

--prodrugs

-- thiopental produce deep and prolonged anaesthesia

-- s. albumin ↓ à protein binding of acidic drugs ↓ à more drug in free form

-- oral anticoagulants can markedly increase prothrombin time because clotting factors already low.

(3) KIDNEY DISEASE :

-- streptomycin, gentamicin à 8th cranial nerve damage

- Clearance of drugs ***that are primarily excreted unchanged*** (aminoglycosides, digoxin, phenobarbitone) is reduced parallel to decrease in creatinine clearance (CLcr)

- Loading dose of such a drug is not altered (unless edema is present) but ***maintenance doses should be reduced*** or dose interval prolonged proportionately.

- **CLcr (patient) ml/min** **dose rate to be reduced by**

50-70	1.5	times
30-50	2	
10-30	3	
5-10	6	

- Plasma proteins, specially albumin, are often low or altered in structure in patients with renal dz.

- Permeability of BBB is increased in renal failure.
- Antihypertensive drugs produce more postural hypotension in renal insufficiency.
- Thiazide diuretics tend to ↓ GFR à ineffective in renal failure

- Potassium sparing diuretics à hyperkalemia à cardiac depression

4) HYPERTHYROIDISM :

--Sensitive to sympathomimetics

--Resistant to morphine

--resistant to inotropic action but more prone to arrhythmic action of digoxin.

(5) CCF

- ↓ drug absorption from git due to mucosal edema
- Expansion of ECF volume à ↑ Vd of some drugs
- Congestion of liver, ↓ GFR à dosing rate of certain drugs should be reduced

(6) OTHERS:

-- Drugs given orally in diarrhea and vomiting may prove to be ineffective.

-- head injury patients are prone to go into respiratory failure with normal dose of morphine.

- MI patients are more to adrenaline and digitalis induced cardiac arrhythmias.

- Antipyretics lower body temperature only when it is raised.